Letters to the Editor . . .

POST-ONCOLYTIC IMMUNITY

During studies on the extraction of substances from induced primary and transplanted rat sarcomata, Aptekman[1] and his associates of the Wistar Institute of Anatomy and Biology, and the Carnegie Institute, Washington, D. C., obtained an alcohol-soluble fraction that inhibited growth of tumor grafts and conferred immunity from further growth of homologous grafts in a large percentage of the treated rats.

All experiments were done on pure inbred strains of white rats. Sarcomas were produced in these rats by the injection of a carcinogenic agent into the right axilla. After the sarcomas had grown to a large size (50 x 25 x 20 mm.) a small amount of the tissue was used for transplantation into other rats of the same strain. The remaining tissue was finely ground, mixed with an equal volume of 95 per cent alcohol, and allowed to stand for 24 hours at refrigerator temperature. The mixture was then filtered and two volumes of 95 per cent alcohol added to the filtrate. After a second refrigeration the resulting precipiate was filtered off. The clear filtrate thus obtained was concentrated to about one-tenth of its original volume by vacuum distillation. The final product was a somewhat cloudy "concentrate" with an alcohol content of from 15 to 26 per cent.

Rats of one litter were implanted on the right side with approximately equal sized grafts of tumors native to their strain. When the grafts had attained a size of about 20 x 8 x 5 mm., part of the rats were injected intratumorally daily with 0.5 to 1 cc. of homologous concentrate. Other rats were left untreated to serve as controls, or were injected with a control solution. Among these controls were: extracts from beef muscle, from normal rat tissue and solutions containing known amounts of alcohol.

Fifty-six of the 58 tumors thus treated were destroyed from three to five and occasionally as many as nine to fourteen injections being required for complete oncolysis. No oncolysis was noted in 45 litter-mates similarly injected with control solutions. Some of the tumors treated with control solutions became necrotic and opened to the surface. Nevertheless, the malignant cells continued to multiply and the tumor increased in size until it brought about the death of the host. Not one of the 25 rats healed by the "concentrate" and kept alive for many months had a recurrence of the tumor.

The remaining 32 healed rats were implanted on the opposite side with a graft of the same type of tumor as that destroyed. The grafts grew in every one of the untreated control rats, but failed to grow in 25 (78.1 per cent) of the 32 rats whose tumors had been destroyed by injections of "concentrate." These 25 apparently immune rats were later implanted with graft of a second sarcoma that had originated in the same strain. Fifteen of these rats proved to be resistant to growth of these heterologous grafts.

Five healed and immune female rats were mated with five healed and immune males. When the offsprings were 30 days old, they and their parents were engrafted with a fragment of the same kind of tumor which had undergone oncolysis in the parent. The grafts grew in every one of the offspring, but did not grow in the parents.

This work is of basic theoretical interest since it is the first experiment in which the injection into tumors of an oncolytic substance has brought about an immunity to tumors homologous to a specific rat strain. Heterologous post-oncolytic tumor immunity was previously reported by Gross,[2] Lewis[3] and others. Attempts to determine the exact mechanism of this post-oncolytic homologous tumor immunity are now in progress.

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"CANCER OR CANCERS?"

Cancer or cancers? Oberling,[5] in his excellent monograph, "The Riddle of Cancer," answers this question in a manner generally satisfactory to students of the subject:

> "To the experimentalist the idea that cancer is a whole group of disorders, each with a different cause, is wholly unsatisfactory since no matter how strongly the etiological dissimilarities be emphasized cancer to him is one disease, and one disease only. He sees always the same cellular derangement, marked by exalted proliferation, invasive growth, and above all the impudent independence that is called autonomy."

Although the tissue in which the cancer cell primarily arises contributes, through local tissue reactivity, a superficial histological definitiveness to the malignant lesion so that gastric carcinoma is, for example, usually distinguishable from carcinoma of the esophagus, the identity of the site of origin becomes less certain as the malignancy of the tumor increases. In other words, as the number of definitive cancer cells within a tumor increases, the lesion bears a decreasing resemblance to the tissue within which it arose so that the most malignant tumors, generally, resemble the tissue of their origin least and each other most.

Modern pathology has generally discarded any but a tentative morphological distinction between carcinoma and sarcoma.[2] Any attempt to sustain rigid distinctions in the classification of the infinite gradations in the exhibition of the notably pleomorphic cancer cell must lead to complete failure. Past efforts in the classification of cancer are reflected in such terms as "carcinosarcoma," "sarcocarcinoma," "sarcomatoides," "pseudo-carcinoma," etc. Even such expansive nomenclature proves inadequate to describe the not uncommon instances in which a carcinomatous exhibition of cancer, is found merging into or metastasizing as sarcoma, or vise versa. Although most exhibitions of cancer in man appear undoubtedly to reflect a common fundamental process, the classification of cancers according to their anatomical site and degree of anaplasticity, of course, remains clinically a practical necessity.

In examining the so-called "etiological dissimilarities" in cancer, a distinction should be made between contributory etiological factors and the final-common-pathway by which the effects of these diverse factors are mediated. Thus we may speak of many etiological agents for inflammation, and yet recognize a chain of morphogenetic phenomena common to them all. If it is true, therefore, that all cancers represent essentially the same morphogenetic process, it follows that careful examination of the nature and etiology of a specific exhibition of cancer

should afford clues as to the property of all malignant tumors.

In a summary which he wrote in 1908, Marchand first pointed out that chorionepithelioma possesses great theoretical importance in regard to tumor formation. At that time the polemic on the maternal vs. the foetal origin of chorionepithelioma had not yet been resolved, though the weight of evidence was already tipping in the direction of Marchand's thesis of 'foetal" origin.

That primary uterine chorionepithelioma represents the cancerization of the maternal host by the trophoblast of the conceptus is now universally accepted. And though the malignancy of this tumor is not exceeded by that of any known exhibition of cancer, it is significant that the so-called malignant cell here is a trophoblast cell (Langhans cell) indistinguishable morphologically or biologically from the same cell in the chorion of normal pregnancy.[6] In other words, primary uterine chorionepithelioma represents the simple overgrowth of the physiologically malignant trophoblast[1] as a result of the lack of a humorally mediated substance by which such overgrowth is prevented in the course of normal gestation. This is shown by the fact that when the trophoblast plus the definitive ambryo are cultured *in vitro* the trophoblast erodes, infiltrates and destroys the latter in, as Maximov phrases it, "the absence of the checking influence of the mother."[4] Thus it is clear that one of the most malignant exhibitions of cancer known may arise without the mediation of "mutations," viruses or chemical carcinogens.

The morphogenesis of primary uterine chorionepithelioma and its metastases is clear. Following the meiosis (gametogenesis) of a diploid totipotent cell, a haploid gasetogenous cell is produced which, in the normal process of reproduction, is activated by fertilization. Following this the trophoblast is segregated from the non-trophoblast cells of the early conceptus: and it is the trophoblast that, through its "physiologically malignant" properties, infiltrates the maternal host to establish an adequate decidua. Failure of the host to check this trophoblastic growth, of course, may result in the overgrowth of chorionepithelioma. It is not, therefore, without significance that such chorionepithelioma represents the only exhibition of cancer in which an introduction of a new cell type does not accompany the so-called malignant change.

It is significant, however, that chorionepithelioma is not always confined to the reproductive organs nor is it found only in the female. Testicular chorionepithelioma as well as primary extra-genital chorionepitheliomas in both sexes present cytotrophoblast that is indistinguishable from that of the normal pregnancy trophoblast. It is generally accepted that testicular chorionepithelioma arise from germ-cells (diploid totipotent cells[2]), but the fact is usually overlooked that such cells must first undergo meiosis to produce the trophoblast-competent gametogenous cell that has, as the only alternative to death, the initiation (by division) of a genetically unique life-cycle through the initial production of trophoblast. It is thus of the utmost theoretical importance that the trophoblast cell has *never* been found outside the canalization of normal pregnancy except as one of the most malignant exhibitions of cancer. And unlike all other cells of the life-cycle, the trophoblast cell is the only cell that has never been found ectopically except as cancer.

In recent years several well authenticated cases of primary extra-genital chorionepithelioma in the male have been reported. Of these a case described by Stowell Sachs and Russell[7] of a primary chorionepithelioma of the pineal gland of a 15-year-old boy is of particular interest, since scrupulous serial examination of the testes apparently ruled out the possibility of an obscured primary testicular growth. The low level of tissue reactivity in the pineal gland and brain probably accounts for the fact that the trophoblast cells were not obscured nor masked as they so frequently are in testicular growths, for example, where the bulk of them may be exhibited in the matrix of somatic tissue of adenocarcinoma, seminoma or sarcoma and where only small nests of overt chorionepitheliomatous cells, plus the cytotrophoblastic prolan in the urine, attest the trophoblastic nature of the malignant component.

A number of primary genital as well as extra-genital chorionepitheliomas have been reported in which the overt trophoblast cells have merged by imperceptible degrees into the "masked" trophoblast of adenocarcinoma or sarcoma—or metastasized as such. And primary sarcoma and adenocarcinoma have been described as metastasizing as chorineonepithelioma. It is clear, therefore, that if we accept the thesis of the fundamental identity of all exhibitions of cancer and understand the morphogenetic phenomena of but one type—chorionepithelioma—it follows that we must ascribe the same phenomena to the remaining types. Besides being Euclidean in its clarity this deduction is consonant with the axiom that cells of the same type arise from preexisting cells of the same type, as expressed in Bard's extension of Virchow's famous dictum of *omnis cellule e cellule* to *omnis cellula e cellula ejusdem generis*. While the trophoblastic nature and diploid-totipotent-cell origin of all exhibitions of cancer is the certain corollary of the concept of the fundamental identity of them all, any alternative to the unitarian thesis, in view of the evidence yielded by chorionepithelioma, will inevitably lead to a *reductio ad absurdum*.

Morphogenetically, then, the common malignant component in all exhibitions of cancer is the trophoblast cell (however masked morphologically) and the common cell of origin is the ubiquitous totipotent cell, the potency of which has been reserved since early cleavage. This simply means that the cancer cell is the most primitive cell in the life-cycle of the animal: that this cell is normally a component of the life-cycle and does not arise through spontaneous generation. This, of course, is consistent with the imperfectly defined and widely held idea of the "embryonic" nature of cancer.[3] And just as the presence of bacteria or other foreign agents in the body can evoke a wide variation in the kinds of tissue reactivity, depending upon the tissue affected, etc., so can the ectopic trophoblast cell elicit a variety of exhibitions of cancer besides frank chorionepithelioma.

The means by which such etiological agents as the chemical carcinogens, certain metabolites, possible viruses, radiation, etc., converge into the final-commonpathway mediating the meiosis of the totipotent cell and the activation of the consequent gametogenous cell to trophogenesis are not fully understood. To say that such action is one of organizer stimuli upon competent cells is merely to restate rather than to explain the phenomenon.

Certainly, further advances in our knowledge of the endocrinology of reproduction promise to answer many questions in the field of oncology; while the means by which the conceptual trophoblast is first checked in its growth and then destroyed in the course of normal gestation, probably offers a very rewarding route for further investigation.

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